another, based on a subgroup of 490 patients from the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) cohort (2), which also concluded that MTWA testing did not predict arrhythmic events or mortality. After reading these reports, how does one act when facing a patient who might be a candidate for an ICD implantation? Should one go ahead with the ICD implantation or resort to testing for MTWA? Does MTWA still have some role to play? One approach is to wait and comfort ourselves with the routine pronouncements that more well-designed studies, enrolling larger number of "representative" patients and with longer follow-up periods, are in order. In reference to the latter, a long follow-up period has its disadvantages, because one should not expect a single, initially carried out MTWA test to be predictive of clinical outcomes of patients afflicted by a changing disease state over a protracted period of time, and thus periodic MTWA assessment (every 6 to 12 months?) might be advisable. Wouldn't this be prudent for other tests (e.g., exercise stress testing), and thus shouldn't this also apply to MTWA evaluation? This reader does not expect any "light in the tunnel" to be forthcoming by resorting to "more studies" with "larger study cohorts" and has put his hopes only in some "tinkering" with the implemented MTWA testing technology. Vast experience indicates that marked alterations of the morphology, amplitude, and polarity of the T waves and J-T intervals are commonplace in both normal subjects and patients. Some of these changes can be traced to alterations in heart rate, but most of them remain unexplained and are encountered in clinically stable individuals. One wonders as to the impact of such changes on the magnitude of MTWA. The magnitude of the MTWA (not reported in the study under consideration [1]) is of significance for both quantitative and qualitative study designs; after all, a cut point of ≥ 1.9 μV is implemented for the characterization of a test as positive/negative/indeterminate. It has been speculated (not shown) that the MTWA magnitude might be T-wave amplitude-dependent (3), and thus it might be of value to adjust the magnitude of the MTWA by the amplitude of the corresponding T waves used in the measurement/calculation of MTWA. Such a notion might be more applicable to the time-domain MTWA methodology using a modified moving average analysis, but it applies in principle to the spectral analytic method. In the latter, one should expect that this "indexing" of MTWA magnitude values should consider the entire J-T interval in some form of representation. However, one should attempt to take the first step (however crude) of "indexing" the MTWA magnitude values by the corresponding T-wave amplitudes. This should be applied separately for patients with normal and prolonged QRS complexes. In this context, it might be of value to the readership for Chow et al. to supply us with the quantitative results of the MTWA of their study and evaluate whether adjusting such MTWA values by the corresponding T-wave amplitudes leads to an MTWA index with worse, the same, or better prognostic power than they have identified in their study.

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Reply

It is true that despite promising early studies, clinical application of microvolt T-wave alternans (MTWA) has become less clear, with both the MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial (1) and the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) substudy (2) failing to demonstrate an association of MTWA with their primary end points. The issue is further muddied by the conflicting results from the ALPHA (T-wave alternans in patients with heart failure) study (3), in which MTWA predicted arrhythmic mortality in nonischemic cardiomyopathy patients. Although the explanation(s) for such divergent findings remain speculative, one possibility is that implantable cardioverter-defibrillator (ICD) shocks, which were used as end points in both the MASTER and SCD-HeFT trials, might be a poor surrogate for arrhythmic mortality due to lack of specificity. In a recent MTWA meta-analysis, Hohnloser et al. (4) concluded that MTWA studies in which ICD penetration was low and that used mortality as the primary end point generally show MTWA to be a powerful predictor of events. The reverse is true for studies such as MASTER and SCD-HeFT, in which ICD penetration was high and which used ICD shock end points.

Where to go from here with respect to MTWA is a matter of differing opinion, but for many, enthusiasm has been replaced by caution. Attempting to improve prediction through refining interpretation of the test (e.g., using MTWA magnitude as a continuous rather than dichotomous index of risk, possibly with adjustment for T-wave amplitude) has conceptual appeal but still requires clinical validation. In the MASTER trial, exploring different heart rate cut-off thresholds for defining positive and negative MTWA test results (i.e., onset heart rate and maximum negative heart rate) did not improve predictive value (5). Retrospective analysis of alternans amplitude as a risk index, as suggested by Dr. Madias, is certainly possible. In principle, additional refinements could also be made. For example, because MTWA is heart rate-dependent, overlap of patient daily heart rate with the onset heart rate for alternans could be a better index of risk than whether alternans is present at an arbitrary heart rate threshold of 110 beats/min. Whether trigger-substrate type relationships exist between MTWA and, for example, ventricular ectopy are largely unknown. Utility of MTWA as a component within a "suite" of noninvasive predictors is also under evaluation in other ongoing studies.

With respect to the concept of serial MTWA testing raised by Dr. Madias, all MASTER patients were in fact required to

undergo annual MTWA testing. We previously reported that annual concordance between MTWA test results was relatively low, and by the end of the study, approximately two-thirds of patients had tested differently at least once (6). This finding supports study designs that include periodic MTWA testing during follow-up.

At a more conceptual level, it is important to recognize the difference between "routine" testing for MTWA and whether MTWA as a biological phenomenon participates in arrhythmia genesis or susceptibility. The optimist might say that we need to improve our understanding of how and when to test for MTWA through future research rather than reject the entire concept altogether.

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